UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/687,060	10/16/2003	Claudine Bruck	B45110C1	8921

7590 05/02/2007

GLAXOSMITHKLINE
Corporate Intellectual Property - UW2220
P.O. Box 1539
King of Prussia, PA 19406-0939

EXAMINER	
HUMPHREY, LOUISE WANG ZHIYING	
ART UNIT	**PAPER NUMBER**
1648	

MAIL DATE	DELIVERY MODE
05/02/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/687,060	BRUCK ET AL.	
	Examiner	Art Unit	
	Louise Humphrey, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-54* is/are pending in the application.

4a) Of the above claim(s) *44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-43 and 45-54* is/are rejected.

7)☒ Claim(s) *32* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the amendment filed 08 February 2007. Claims 1-31 are cancelled. Claim 54 is added. Claims 32-54 are pending.

Response to Arguments

Claim Rejections - 35 U.S.C. §112

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The New Matter rejection of claim 41 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement is **withdrawn** in consideration of Applicants' argument that Example 4, page 21, indicates the carboxymethylation step in the purification of the fusion protein.

The rejection of claims 32-43 and 46-53 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification commensurate in scope is **maintained** and extended to new claim 54.

Examiner's rejection in the Action mailed on 08 August 2006 is as follows:

Enablement is considered in view of the Wands factors (MPEP §2164.01(a)). The claims are drawn to an immunogenic fusion protein comprising Nef-mutant Tat. The process of site-directed mutagenesis is well known to one skilled in the art for making the claimed Tat mutant protein and Nef-mutant Tat fusion protein. However, the claims encompass any mutations in the active site and RGD motif. Therefore, the claims also encompass a mutant Tat with an entirely different epitope structure around the active site and RGD motif. No working example that demonstrates the immunogenicity of any Nef-mutant Tat fusion protein is disclosed in the specification.

The specification is limited to the description of only one Tat mutant (Lys41Ala, Arg78Lys, Asp80Glu) without disclosure of the immunogenic effect of this mutant Tat alone or when it is fused to the C-terminal of Nef. There is no guidance to any conserved structure or epitope conformation for maintaining the desired immunogenicity. The specification nowhere describes whether SEQ ID NO: 13, 17, or 21 comprises a wild type or mutant Tat fused to Nef. The art lacks predictability in making mutations that will result in a desired outcome of being immunogenic and providing a protective effect (Corchero *et al.*, 1996; Abaza *et al.*, 1992). Cochero *et al.* (1996) discloses that the antigenic site can display different antigenicity depending on the global construction of the chimeric protein that contains VP1. Long distance influences occurring in the fusion protein can also determine the antigenic behavior of a small peptide exposed in its natural framework (Corchero *et al.* last ¶). An immunogenic Nef-mutant Tat fusion protein is not considered routine in the art and, without sufficient guidance to elicit immunogenic effects, the experimentation left to those skilled in the art is to characterize every Nef-mutant Tat fusion since it is not known what immunogenic effect each mutation at the active site and RGD motif has on the fusion protein.

Applicants argue that: (1) the amended claims are directed to compositions that include fusion proteins that include Nef and/or Tat polypeptides linked to specific derivatives (mutated versions) of Nef and/or Tat polypeptides and do not encompass fusion proteins "with an entirely different epitope structure around the active site and RGD motif;" (2) the working examples disclose a Nef-Tat fusion that includes a derivative of Tat that has a deletion of amino acids from the C-terminal end or a C-terminal histidine tail (Example 2, page 15) and a Nef-Tat fusion protein with amino acid substitutions in the active site region and in the RGD motif (Example 3); (3) the specification provides guidance with SEQ ID NO:13, a fusion protein of Nef and Tat without modifications, and SEQ ID NO:25, a fusion protein comprising a modified Tat; and (4) the amended claims are directed to fusion proteins with a specific amino acid sequence.

Applicant's arguments have been fully considered but are not persuasive. While the amended claims recite four specific types of polypeptides (an HIV Tat/Nef protein; a protein comprising amino acids 2-86 of Tat or amino acids 2-206 of Nef, a Tat/Nef with a C-terminal His tail; and a Tat that bears mutations K41A in the active site, and R78K and D80E in the RGD motif), the word "derivative" and the phrase "a Tat/Nef comprising a deletion, addition or substitution of one amino acid" do not limit the invention to "specific derivatives" as Applicants assert. The claims and the specification do not specifically define the word "derivative" as proteins with certain specific modifications. Therefore, Applicants' assertion that the claims do not encompass fusion proteins "with an entirely different epitope structure around the active site and RGD motif" lack evidentiary basis. The disclosure of exemplary fusion proteins in the working examples and in SEQ ID NO:13 and SEQ ID NO:25 do not purport to the inordinate number of variants encompassed by the genus of "a derivative thereof" and "a Tat/Nef comprising a deletion, addition or substitution of one amino acid." The instant claims encompass proteins with any type of modification at any of its amino acid position. The claims do not limit to a specific amino acid sequence for a Nef derivative. Likewise, the claims do not limit to a specific amino acid sequence for a Tat derivative except claims 35 and 54. The recitation "an amino acid sequence" in claim 53 reads on a portion of the specific sequence identified by the SEQ ID NO whereas the previous recitation "the amino acid sequence" reads on the full length SEQ ID NO. It is highly unpredictable whether each variant of the claimed broad genus would maintain its immunogenic epitopes and is biologically inactive for reasons set forth in the previous Action as repeated above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 39 under 35 U.S.C. §103(a) as being obvious over Schluesener *et al.* (1996) in view of Hincula *et al.* (1997) is **withdrawn** in response to the amendment.

The rejection of claims 32-34, 37, 38, and 51 under 35 U.S.C. §103(a) as being obvious over Schluesener *et al.* (1996) in view of Hincula *et al.* (1997) is **maintained** and extended to claim 36 in response to the amendment.

The instant claims, as amended, read on an immunogenic composition comprising a fusion protein of HIV Tat and Nef protein and optionally a fusion partner.

Examiner's rejection in the Action mailed on 05 June 2006 is as follows:

Schluesener teach linking HIV Tat to three pathogenic T-cell epitopes in admixture with a physiological saline (p.259, left column, RESULTS, 2nd ¶), which is a pharmaceutically acceptable excipient, in order to make an immunogenic composition. The reference teaches that this fusion combination improves their immunogenicity. The reference does not teach fusion of Tat with Nef.

Hinkula *et al.* teach a composition of Nef, Tat or Rev as an immunogen. The reference also teaches that due to the polymorphism found in the human population, an effective vaccine will require the combination of many proteins or glycoproteins (page 5538 last paragraph). The reference does not teach a Tat-Nef fusion protein.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the polyvalent Tat peptide of Schluesencer by additionally fusing the Nef protein of Hincula *et al.* The skilled artisan would have been

motivated to do so to increase the immunogenicity of Nef via Tat-mediated targeting of proteins, which improves cellular uptake of recombinant peptide vaccines such as Nef. There would have been a reasonable expectation of success, given that fusion with Tat peptide improves the immunogenicity of T-cell epitopes, as taught by Schluesener, and provided that Nef and Tat each can induce immune reactivity, as taught by Hinkula. Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Applicants argue that: (1) Schluesener does not teach or suggest linking HIV Nef to Tat; (2) Schluesener teaches that the peptides fused to Tat are immunosuppressive, rather than immunogenic; and (3) Hincula does not disclose a fusion protein.

Applicant's arguments have been fully considered but are not persuasive. Although Schluesener does not teach linking HIV Nef to Tat, Schluesener teaches a fusion protein comprising Tat, a cell-binding domain that mediates targeting of other proteins, fused to a heterologous protein, which is encompassed by the limitation "a fusion partner" in the instant claims. Such a fusion of Tat to the heterologous protein might effectively induce immune responses or could potentially tolerize the immune system. See page 258, Introduction. The effect of the fusion depends upon whether the heterologous protein is an immunogen or a tolerogen. The teaching of immunosuppressive Tat fusions cited by the Applicants demonstrates the latter. However, Applicants seem to have focused on the part of this reference that is irrelevant to the instant invention. Although Hincula does not disclose a fusion protein, Hincula discloses that HIV-1 regulatory proteins Nef, Tat, and Rev induce immune responses and can be combined to induce potent immune responses of both the B-cell and the Th1 cell pathways. See last ¶ on page 5538. Therefore, Schluesener and

Hincula both provide the motivation to fuse Tat with Nef to induce immune response to a heterologous protein that is further fused to Tat-Nef protein.

The rejection of claim 40 under 35 U.S.C. §103 as being obvious over Schluesener *et al.* (1996) in view of Hincula *et al.* (1997) and further in view of Rosin-Arbesfeld *et al.* (1994) is **maintained**.

The instant claims, as amended, read on an immunogenic composition comprising a fusion protein of HIV Tat and Nef protein and a Histidine tail.

Examiner's rejection in the Action mailed on 08 August 2006 is as follows:

The relevance of Schluesener and Hincula et al. is set forth above. Neither reference discloses a His tail.

Rosin-Arbesfeld *et al.* suggest synthesizing a Tat protein with a His tail. See abstract.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the fusion protein of Schluesener by adding Nef protein as taught by Hincula *et al.* and a His tail as taught by Rosin-Arbesfeld *et al.* The skilled artisan would have been motivated to do so for the ease of purification of a His-tagged protein by metal affinity chromatography. There would have been a reasonable expectation of success, given the yield of protein purification and the potent activity of the purified protein, as taught by Rosin-Arbesfeld *et al.* Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Applicants argue that Rosin-Arbesfeld does not teach a C-terminal His tail. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the feature upon which applicant relies (i.e., C-terminal) is not recited in the rejected claim 40. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Although

claim 32 recites a Tat with a C-terminal His tail as one of the group of Tat proteins to select from, the claim is not limited to the embodiment of Tat with a C-terminal His tag only. Therefore, the limitation of C-terminal is not given weight in this rejection.

The rejection of claims 42, 43, and 45-50 under 35 U.S.C. §103 as being obvious over Schluesener *et al.* (1996) in view of Hincula *et al.* (1997) and further in view of Bomford *et al.* (1992) is **maintained**.

The instant claims, as amended, read on an immunogenic composition comprising a fusion protein of HIV Tat, Nef protein, HIV gp160 or gp120, and a Th1 inducing adjuvant.

Examiner's rejection in the Action mailed on 08 August 2006 is as follows:

The relevance of Schluesener and Hincula *et al.* is set forth above. Neither reference discloses a HIV gp160 or gp120 or an adjuvant.

Bomford *et al.* teach an immunogenic composition comprising HIV gp120 and an adjuvant, saponin, formulated with a squalene-in-water emulsion. The composition induced Th1 response in mice. See Abstract.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the fusion protein of Schluesener by adding Nef protein as taught by Hincula et al. and replacing the pathogenic peptide and formulation of Schluesener with HIV gp120 and the adjuvant formulation as taught by Bomford *et al.* The skilled artisan would have been motivated to do so to increase the immunogenicity of HIV gp120 via Nef and Tat-mediated targeting of proteins, which improves cellular uptake of recombinant peptide vaccines. There would have been a reasonable expectation of success, given the potent immune response induced in mice by the adjuvant and oil-in-water formulation of HIV gp120, as taught by Bomford *et al.* Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Applicants argue that merely because Bomford's adjuvant system of saponin and oil-in-water emulsions is useful in combination with gp120 is not predictive that it will be

effective and favorably be combined with the claimed Nef/Tat fusion proteins. Applicants' arguments have been fully considered and are not persuasive. There is a reasonable expectation of success because Hincula disclose that Nef and Tat can induce potent immune response. Therefore, absent evidence to the contrary, it is obvious to combine the saponin adjuvant in an oil-in-water emulsion with the Tat-Nef fusion and gp120 into a composition that will be effective at inducing immune response.

New Claim Objections/Rejections Necessitated by Amendment

Claim Objections

Claim 32 is objected to because of the following informalities: the ":" after the phrase "an HIV Tat protein" should be replaced with ";". Appropriate correction is required.

Claim Rejections - 35 USC § 112, 2nd ¶

The following is a quotation of the second paragraph of 35 U.S.C. §112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32-43 and 45-54 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 32 and 51 refer to amino acid positions 41, 78 and 80 without indicating which HIV serotype or clone and what sequence is the reference for the position numbers. HIV-1 and HIV-2 differ genotypically and phenotypically. Furthermore, it is

unclear whether the claims are drawn to HIV-1 Tat and Nef proteins, HIV-2 Tat and Nef proteins, or proteins of both subtypes. This rejection affects all dependent claims.

Claim 39 recites the limitation "the fusion partner" in the claim. There is insufficient antecedent basis for this limitation in the claim.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Contact Information

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey, Ph.D. whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9:30 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, can be reached at 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Jeffrey Parkin, Ph.D.
Primary Examiner
23 April 2007

Louise Humphrey, Ph.D.
Assistant Examiner